Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials

CRD summary
The review concluded that the suggested beneficial effect of statins on atrial fibrillation from shorter-term studies was not supported by evidence from larger-scale trials. The authors’ conclusions appeared to reflect the evidence, but it should be borne in mind that the two datasets (long-term and short-term) were clinically and methodologically very different.

Authors’ objectives
To investigate whether longer-term treatment with statins can reduce the risk of atrial fibrillation.

Searching
MEDLINE (from 1966), EMBASE (from 1985) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to October 2010 without language restrictions; search terms were reported. Reference lists of included studies were searched. Unpublished data were sought from investigators.

Further searches were made for shorter-term studies based on the search results of two meta-analyses published in 2008, which were updated to October 2010.

Study selection
Randomised controlled trials (RCTs) that either compared a statin with a control regimen or compared different statin doses were eligible for the review. Studies had to randomise at least 100 participants and have a treatment duration (and follow-up) of at least six months. Studies of any type of participant or outcome were eligible.

The included interventions were atorvastatin, simvastatin, rosuvastatin, pravastatin, lovastatin and fluvastatin. Comparators were placebo, usual care, no treatment, a different statin and a different dose of atorvastatin or simvastatin. Types of study populations varied. Most short-term studies were of patients for whom cardiac surgery or electrical cardioversion was planned (and who had a higher underlying risk of atrial fibrillation compared to longer-term trials). Mean age ranged from 61 to 73 in short-term trials and between 51 and 75 in longer-term trials. Most participants were male. Events for short-term studies were mostly captured using continuous electrocardiographic monitoring. Events for longer-term studies were mostly captured via (largely unpublished) routine adverse event data.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Risk of bias was evaluated using Cochrane methods by assessing criteria of sequence generation, concealment of allocation sequence, blinding, incomplete outcome data, selective outcome reporting and any other potential sources of bias. Studies were categorised as having low, unclear and high risk of bias.

The authors did not state whether the risk of bias assessment was carried out in duplicate.

Data extraction
Intention-to-treat data were extracted in order to calculate Peto odds ratios (OR) with 99% confidence intervals (CI) for individual trials. Investigators were contacted for unpublished atrial fibrillation event rates.

The authors did not state whether data were extracted in duplicate.
Methods of synthesis
Meta-analyses were performed to calculate pooled Peto odds ratios with 95% CIs using a fixed-effect model. Statistical heterogeneity was assessed using $X^2$. Subgroup analyses were performed on various different types of population. Sensitivity analyses examined the effect of high risk of bias status, use of a random-effects model and the exclusion of outlier studies. Subgroup analyses explored the effect of previous disease and whether events were new or recurrent.

Results of the review
Forty-two RCTs were included in the meta-analyses: 13 short-term RCTs (n=4,414 patients, follow-up ranged from 0.02 to 0.42 years) where the risk of bias was low in five trials, high in four trials and unclear in four trials; and 29 longer-term RCTs (n=134,755, follow-up ranged from one to 5.2 years) where the risk of bias was low in all trials except one.

Short-term RCTs: Statin treatment reduced the incidence of atrial fibrillation (OR 0.61, 95% CI 0.51 to 0.74; 13 RCTs). There was significant statistical heterogeneity ($p<0.001$).

Longer-term RCTs: Statin treatment was not associated with a significant reduction in atrial fibrillation when compared with control (0.95, 95% CI 0.88 to 1.03; 22 RCTs). There was no evidence of significant heterogeneity. The difference between the pooled results for shorter- and longer-term trials was significant ($p<0.001$).

Trials of more intensive versus standard statin regimens (28,964 randomised patients and 1,419 events) yielded similar results (OR 1.00, 95% CI 0.90 to 1.12; seven RCTs). There was an indication of statistical heterogeneity ($p=0.05$).

Sensitivity analyses did not significantly alter the results. Subgroup analyses suggested neither evidence that statins prevented first diagnosed atrial fibrillation events nor that the effect of statin treatment differed according to previous disease status.

Authors’ conclusions
The suggested beneficial effect of statins on atrial fibrillation from published shorter-term studies was not supported by a comprehensive review of published and unpublished evidence from larger-scale trials.

CRD commentary
The review addressed a clear primary question supported by appropriate eligibility criteria (albeit criteria/definitions for the shorter term/smaller scale studies were not prespecified). Three electronic databases and reference lists were used to identify studies. There were no language restrictions. The authors did not report specific details of how the pre-2008 shorter-term studies were identified. There was no reported search to specifically identify unpublished studies, but unpublished data from published studies were sought. Suitable methods were employed to reduce risks of reviewer error and bias for the study selection process; the authors did not report on whether such methods were used to assess study quality and extract data. Study quality was assessed and used in interpreting the results of the meta-analyses. Comprehensive study details were provided. Appropriate methods were used to pool data and assess statistical heterogeneity. The authors acknowledged heterogeneity between the shorter- and longer-term trials and their decision not to pool all results was appropriate. The longer-term trials were reviewed in a more systematic way than the shorter-term trials.

The authors’ conclusions appeared to reflect the evidence, but it should be borne in mind that the two datasets (long-term and short-term) were clinically and methodologically very different.

Implications of the review for practice and research
Practice: The authors stated that statins could not be recommended for prevention of incident or recurrent atrial fibrillation.

Research: The authors stated that future well-designed randomised trials could explore the effect of statins on atrial fibrillation in populations of patients and select outcomes that were relevant to patients and healthcare providers.
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